

REMARKS/ARGUMENTS

Claims 45, 46 and 61 have been amended, claims 63-65 withdrawn and claim 47 has been cancelled.

I. Examiner Interview Summary

Applicants wish to thank Examiner Bo Peng for the courtesy extended to Applicant's representatives in conducting a telephone interview with Ian Rourke, Brendon Coventry, Gary Connell and Robert Traver on February 10, 2011, at which time the inventive methodology and potential claim amendments were discussed. The examiner's suggestions have been incorporated in this Response.

II. Overview

Before addressing the prior art rejection, Applicant will provide background information relevant to understanding the present invention and its significance as an advance in the field of cancer therapy. Cancer continues to be one of society's major health problems. "Indeed, the age-adjusted mortality rate for cancer is about the same in the 21st century as it was 50 years ago, whereas the death rates for cardiac, cerebrovascular, and infectious diseases have declined by about two-thirds." (Varmus, H. *Science*. 2006;312 (5777):1162-1165) "By current estimates, approximately one in two men and one in three women—more than 40 percent of the U.S. population—will develop cancer at some point in their lives. In 2008, more than 1.4 million new cases are expected, and more than 565,000 people will die from cancer. Despite declaring a national war on cancer in 1971 and investing many billions of dollars since then to understand and defeat cancer, our success against the disease in its many forms has been uneven and unacceptably slow." U.S. President's Cancer Panel Executive Summary 2008. "[A] 1 percent reduction in cancer mortality would be worth \$500 billion," *The Journal of Political Economy*, Vol. 114, No. 5 (October 2006), pp. 871-904.

As summarized in the Declaration of Dr. Brendon J. Coventry (Coventry Decl.), filed with this Amendment and Response, conventional therapies for cancer include chemotherapy, radiation, and surgery. (Coventry Decl. ¶ 2) The intended mode of action of conventional therapies is to either kill (e.g., by chemotherapy) or remove (e.g., by surgery) cancer cells.

(Coventry Decl., ¶ 2) The complete response rates from clinical trials with anti-cancer drugs has been remarkably consistent (and low) between different cancers, suggesting an underlying factor relevant to all cancers and treatments. See Table 1 of the instant application, reproduced here:

TABLE 1

Complete Response Rates Resulting from Clinical Trails with Anti-Cancer Drugs against Various Cancers.		
Cancer Type	Complete Response Rate (%)	Number of Trials
Mesothelioma ^a	5.1	10
Gastric ^b	7.33	15
Hepatocellular ^c	6.6	8
Pancreatic ^d	7.35	4
Melanoma ^e	7.5	15
Prostate ^f	5.15	7
NSC Lung ^g	5.85	6
Breast ^h	7.36	19
Ovarian ⁱ	8.2	15
Colorectal ^j	6.85	28
Miscellaneous ^k	6.0	17

As can be seen from Table 1 above, there is considerable room for improvement above the previous 5-8% complete response rate for a wide variety of cancers and treatments. As evidenced by the present specification and post-filing data described herein, the claimed invention enhances the chances of effectively treating cancer through the use of a method to determine the most efficacious time to administer the cancer treatment to the patient. The inventor of the present application has established that the underlying factor relevant to all cancers is that the immune system is persistently cycling in cancer patients. Thus, if a cancer patient is administered a given therapy at a random time, there is a only small fixed time within the cycle of the immune system in which the cancer therapy will have maximal effect (about 5-7% of the time as summarized in Table 1).

Based on this understanding, the present invention provides a new paradigm in the treatment of cancer, dependent upon manipulating the immune system of cancer patients to identify and kill cancer cells. "A cure for cancer is not about killing dividing cancer cells the way we have been thinking about it in the past, but appears to be the way immune cells are being killed, depending on the timing of the administration of our therapies," Brendon Coventry in *Are We Ready for the World's Biggest Paradigm Shift in Cancer Therapy?*, Bioshares, Number 372, 13 August 2010. (Coventry Decl., ¶ 3)

III. Amendments to the Pending Claims

In this Amendment and Response, Applicant has amended claims 45, 46 and 61 and added new claim 76 and cancelled claim 47. These amendments to the pending claims clarify that the claimed methods are used in the treatment of a cancer in cancer patients while additionally specifying that the patient is monitored for a marker of immune system activity in order to identify when regulator T cell numbers are increasing in the immune system cycle. Further, these amendments clarify the agents that are to be administered to the cancer patient as well as the intended effect of administering the agent at the identified time in the immune system cycle. Support for these amendments can be found at least at page 3, line 16 through page 4, line 14; page 4, lines 28-31; and page 7, lines 29-31 of the application, as filed. As such, Applicant submits that these amendments provide greater clarity and specificity to the claimed methods while no new matter has been introduced into the application.

IV. Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained rejection of claims 45-47, 49-50, 58, 59, 61 and 62 under 35 U.S.C. § 103(a) as being unpatentable over WO 2003/068257 (WO'257) in view of Huber et al. (Cancer Res. (1980) 40:3484-90). The Examiner characterizes Huber et al. as teaching a continued cycling of cytolytic and suppressive immune cells in immune responses in animals. The Examiner states that while Huber et al. does not actually show continued cycling beyond a first cytolytic phase, a first suppressive phase, and an additional cytolytic phase, this appears to be due to the deaths of the animals rather than an indication that cycling terminates after three

phases. The Examiner then characterizes the WO'257 reference as teaching a benefit to administering certain agents at time points where the suppressor cells begin to become more active. The Examiner concludes it would have been obvious to apply the knowledge of cycling described by Huber et al. to predict the most opportune time for repeated administration of the agents of the WO'257 reference, by first monitoring the patient to determine the approximate timing of the various phases in the cytolytic/suppressive activity cycle. Additionally, the Examiner contends that Huber et al. teaches the existence of the cytolytic/suppressive cycle making it apparent that repeated administration of agents inhibiting the suppressor cell activity would be required.

No *Prima Facie* Case of Obviousness

Applicant respectfully traverses this rejection on the basis that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicant submits that the cited references, alone or in combination do not disclose the following claim elements: analyzing the results from monitoring to understand the dynamics of the persistent immune system cycling (step ii, claim 45) nor administration of an agent when regulator cell numbers and/or activity are increasing in the cycle (step iii, claim 45). WO'257, by the Examiner's admission, does not teach or suggest immune system cycling and therefore, cannot show either of these elements, which require an understanding of such cycling.

In regard to Huber et al., Applicant maintains the position that Huber et al. fails to teach persistent cycling of the immune response and therefore, cannot disclose either of these elements. The Examiner, in acknowledging that Huber et al. does not actually show continued cycling, states that such lack of teaching appears to be due to the deaths of the animals rather than an indication that the cycling terminates after the disclosed phases.

However, the disclosure of Huber et al. contradicts such a conclusion. In support of positions in this Amendment and Response, Applicant is submitting the Declaration of Dr. Brendon J. Coventry under 35 U.S.C. § 132 ("Coventry Decl."). Dr. Coventry has significant experience in the treatment of cancer using a variety of techniques and therefore, possesses at least a level of ordinary skill in the art. Dr. Coventry reviewed Huber et al. and disagrees with the position in the Office Action and concludes instead that data in Huber do not support the

position that Huber et al. suggests persistent cycling. (Coventry Decl. ¶ 7) Specifically, the fourth and fifth graphs of Chart 1 in Huber show rats surviving to 24 and 32 days, without showing additional cycling occurring from day 16 onward. Further, cycling should have been seen in the time period from day 16 to either day 24 (fourth graph) or day 32 (fifth graph). (Coventry Decl. ¶ 7.a.) The reason Huber did not show persistent cycling (perhaps insufficient sampling or sampling at the wrong times) is not clear, but at least in the fourth and fifth graphs of Chart 1, the rats survived long enough that cycling should have been observed if it were occurring in these animals. (Coventry Decl. ¶ 7.a.) The fact that Huber did not show persistent cycling in those graphs would have suggested to a skilled person that persistent cycling of the immune system does not occur (Coventry Decl. ¶ 7.a.) Moreover, Huber et al. specifically states that the cellular immune response “can be divided into 3 sequential phases: an early cytolytic phase; a period of noncytotoxicity; and a second of late cytolytic phase (Chart 1).” Huber et al. then repeatedly refers to three phases of the immune response. (See, for example, page 3487 of Huber et al. and page 3489, second paragraph; “These observations suggest that the 2-cytolytic phases...”) Further, on page 3487, top of right column, Huber et al. refers to the first phase of the immune response as “the first wave” and the second phase as “late cytotoxic cells.” Huber et al. argues that these two phases were different and distinct from each other. Thus, it is evident from Huber et al. that those of skill in the art (i.e. the authors themselves) did not recognize a persistent cycling in the immune system cells of these animals in review the data they had collected and presented.

Huber et al. also teaches that sera obtained within 16 days of immunizing animals with MTA cells was more effective at blocking the first wave of cytotoxic cells, whereas sera obtained after 16 days was more effective at blocking late cytotoxic cells. The fact that early and late phase cytotoxic lymphocytes in Huber were inhibited differently by suppressor cells (Huber, 3487-88), suggests that these two phases are not the same, and Huber therefore teaches that these are separate phases. (Coventry Decl. ¶ 7.b.) From this result, a skilled person would infer that these two phases are not recurring as part of any persistent cycle. (Coventry Decl. ¶ 7.b.) In discussing these results, Huber et al. states that “serological factors blocking the CMC reaction are detected within a short time of tumor injection (approximately 4 to 8 days) and, in various forms, *persist until animal death*” (emphasis added; see page 3489, first paragraph of left

column). Thus, Huber et al. clearly states that the immune response to an injected tumor is bi-cyclic, and does not undergo persistent cycling, as characterized by the Examiner.

In further regard to the issue of cycling, a number of researchers over the years have studied the immune response to tumors. These are principally using implanted tumours in animal models. (Coventry Decl. ¶ 8) Robert J. North has published in this area and several of his publications are submitted as part of an information disclosure statement concurrently with the filing of this Amendment and Response. For example, in North and Bursucker (1984), Fig. 10 is a diagrammatic representation of the immune response to a progressive immunogenic tumor of the type represented by the meth-A fibrosarcoma. (Coventry Decl. ¶ 8) This figure suggests just a single peak of effector cells in response to the tumor and not cycling of effector cells. (Coventry Decl. ¶ 8)

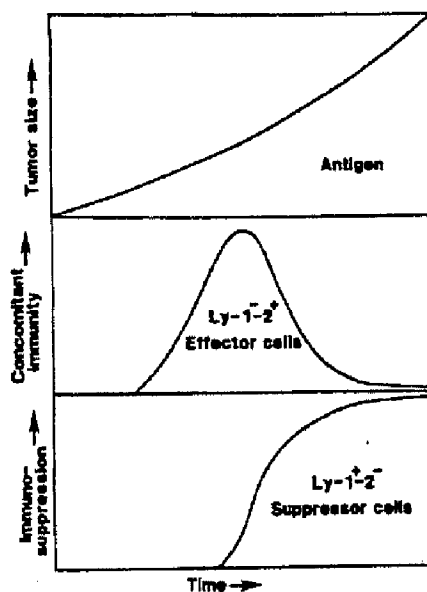


FIGURE 10. Diagrammatic representation of the immune response to a progressive immunogenic tumor of the type represented by the meth A fibrosarcoma. After the tumor reaches a critical minimum size it provides enough antigen to evoke the generation of $Ly-1^{-}2^{+}$ effector T cells. However, a short period of additional tumor growth provides antigenic conditions that favor the generation of $Ly-1^{+}2^{-}$ suppressor T cells that function to down-regulate the production of $Ly-1^{-}2^{+}$ effector T cells. Consequently, not enough effector T cells are made to destroy the tumor.

However, Applicant submits that even assuming, *arguendo*, that Huber et al. does disclose cycling of the immune system, Huber et al. does not teach or in any way suggest (i)

analyzing the results from monitoring to understand the dynamics of persistent immune system cycling, nor (ii) administration of a treatment when regulator cell numbers and/or activity are increasing in the cycle. Therefore, Applicant submits that a *prima facie* case of obviousness has not been established because not all of the claimed elements are shown by the combined references.

Additionally, Applicant submits that even if Huber et al. is understood to teach persistent cycling, which Applicant disputes, there is no rationale or motivation to combine the teachings of Huber et al. and the WO'257 reference.

“The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art.” MPEP § 2143.01, III (citing *KSR v. Teleflex*, 550 U.S. 398 at 417 (2007)). Additionally, it is well-established that “if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” MPEP § 2143.01, V (citing *In re Gordon*, 733 F.2d 900, (Fed. Cir. 1984)).

The Examiner suggests that, based on disclosure of WO'257, the patient will be monitored for some period of time, which could be long enough to detect a cycle, and therefore practicing the method of WO'257 would include detecting a cycle. However, Applicant contends that modifying the references as suggested by the Examiner renders them unsatisfactory for their intended purposes. As is clear from WO'257, the window between resetting the immune system and administration of an agent is relatively narrow, such as about two weeks following the “resetting.” (Coventry Decl., ¶ 5.b.) See Example 1 in which a dramatic difference between administration of an agent at 14 days vs. 15 days was seen. (Coventry Decl., ¶ 5.b.) WO'257 teaches that the only means by which to take advantage of the phenomenon of the beneficial administration of agents when suppressor cells begin to become more active was to “reset” the immune system by, for example, reducing the tumor load so that there was some tumor antigen based stimulation of effector cells and then immediately look to emerging effector and regulator T cell populations to treat the patient, such that effector cell activity was maintained to some degree while reducing or minimizing regulator cell activity. (Coventry Decl., ¶ 5.a.) By modifying WO'257 as suggested by the Examiner to arrive at the claimed invention, a skilled

person would be acting contrary to the teaching of WO'257, which requires resetting the immune system, such as by reducing tumor load, and then treating the patient as soon as suppressor cells begin to become more active. In contrast, the present invention requires that a patient is monitored for at least one cycle of the immune system without resetting. (Coventry Decl., ¶ 5.c.)

Moreover, the present invention is significantly distinct from the resetting invention of WO'257 because WO'257 requires a resetting step, whereas the present invention does not, and the present invention requires monitoring a patient for at least one cycle of the immune system, whereas WO'257 does not. (Coventry Decl., ¶ 5.d.) Thus, there would be no reason or benefit to determine the characteristics of a cycle in WO'257 because the key parameter is to administer an agent after resetting once suppressor cells become active. For the foregoing reasons, Applicant submits that there is no reason or motivation to combine the references and therefore, a *prima facie* case of obviousness has not been established.

Applicant further submits that the references should not be combined because there would have been no reasonable expectation of successfully treating cancer patients based on the combination of Huber et al. and the WO'257 reference. A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). In this instance, Applicant submits that the claimed invention would not be viewed by a skilled person as a combination that would yield predictable results. In fact, the method of the present invention has been considered to be a "paradigm shift" in treatment of disease. (Coventry Decl., ¶ 3) More specifically, Dr. Coventry states that "[t]he invention claimed in the present application is a dramatic change in approach for the treatment of cancer, in other words, a paradigm shift from existing treatment concepts. In an article in Bioshares entitled *Are We Ready for the World's Biggest Paradigm Shift in Cancer Therapy?*, Dr Coventry is quoted as saying 'A cure for cancer is not about killing dividing cancer cells the way we have been thinking about it in the past, but appears to be the way immune cells are being killed, depending on the timing of the administration of our therapies.' Conventional therapies have focused on killing cancer cells, whereas this invention is focused on killing certain immune cells

by understanding the dynamics of persistent immune system cycling within a patient.”
Therefore, the elements of the present invention cannot properly be characterized as the combination of elements by known methods with no change in their respective functions to yield nothing more than predictable results.

V. Secondary Considerations of Non-Obviousness

As evidence of non-obviousness of the present invention, the Coventry Declaration in Paragraph 9 describes data from a poster presentation at the 2009 American Society of Clinical Oncology (ASCO) Annual Meeting. (Individualized (Timed) Delivery of Standard Chemotherapy as a means of immune reconstitution in patients with metastatic melanoma, Quevedo et al., Poster presented at 2009 ASCO Annual Meeting). As stated by Dr. Coventry, the data in this poster are evidence that practice of the presently claimed invention provides superior results compared to conventional cancer therapy. (Coventry Decl., ¶ 9) More specifically, of twelve patients with metastatic melanoma, two patients treated in accord with the present invention (chemotherapy administered at a time in the immune system cycling when regulator cell numbers and/or activity are increasing) remained progression free for more than two years. In contrast, nine patients not treated in accord with the present invention (chemotherapy administered at a time in the immune system cycling when regulator cell numbers and/or activity were not increasing) had tumor progression in less than five months. One of the patients was not treated because of rapid tumor progression.

As further evidence of non-obviousness, Applicant provides the following media reports and communications from the scientific community.

1. “AM – Cells switched off for tumour treatment”, ABC Online, downloaded from <http://www.abc.net.au>, 4/05/2009 (Attachment 1).
2. “Scientists manipulate immune system to fight cancer”, ABC News, downloaded from <http://www.abc.net.au>, 23/03/2009 (Attachment 2).
3. “Melbourne researchers pioneer radical ovarian cancer treatment, Nick Miller, The Age, Melbourne, Australia, 24/03/2020 (Attachment 3).
4. “Cancer discovery heads for trials”, Rebecca Urban, downloaded from <http://www.theage.com.au>, 24/03/3009 (Attachment 4).

5. "Cancer 'Code' is Cracked", Lucy Johnston, downloaded from <http://www.express.co.uk>, 15/04/2009 (Attachment 5).

6. Declaration by Professor Andrew Wilks FTSE, 8 November 2007 (Attachment 6).

7. Letter from Svetomir N. Markovic, M.D., PhD, 22 May 2007 (Attachment 7).

8. Letter from Svetomir N. Markovic, M.D., PhD, 3 October 2005 (Attachment 8).

9. Declaration by Dr. Andrew Robinson, 18 April 2010 (Attachment 9).

The above-referenced documents illustrate the impact of Applicant's invention not only in the media, but within the community of those skilled in the art. More specifically, Items 1 and 2, for example, illustrate that it was the fundamental recognition that the immune system is cycling in response to cancer that led to the present inventor's discovery that the immune system can be manipulated by targeting T cells that regulate the immune response. Likewise, Items 6-9 illustrate that this invention is being accepted by practitioners in the field, as well as statisticians.

VI. Rejection for double-patenting

The Examiner has maintained his rejection of claims 45-47, 49-50, 58, 59, 61 and 62 on the ground of nonstatutory, obviousness-type double patenting, as being unpatentable over claims 1-4, 6, 10-13, and 15 of co-pending Application No. 12/233,369 in view of Huber et al. For the reasons discussed above with respect to the differences between the present invention and WO'257 (which corresponds to Application No. 12/233,369), Applicant submits that the double patenting rejection is not proper and should be withdrawn.

Appl. No. 10/576,981
Amdt. dated May 19, 2011
Reply to Office Action mailed June 3, 2010

VII. Conclusion

Based upon the foregoing, Applicant believes that all pending claims are in condition for allowance and such disposition is respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

Respectfully submitted,
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Date: May 19, 2011



ABC Online

AM - Cells switched off for tumour treatment

[This is the print version of story <http://www.abc.net.au/am/content/2008/s2513799.htm>]

AM - Thursday, 12 March , 2009 08:09:00

Reporter: Rachael Brown

TONY EASTLEY: Melbourne researchers think they've found a way to turn off the cells that prevent cancer patients' immune systems from beating previously untreatable tumours.

The Women's Cancer Foundation and Monash University have just begun an 18-month trial using low-dosage chemotherapy pills. They say it could save hundreds of thousands of lives each year.

Rachael Brown spoke to oncologist, Professor Michael Quinn from Melbourne's Royal Women's Hospital.

MICHAEL QUINN: What we're hoping is that by using this particular method of synchronising the patient's own immune system that we'll be able to get better responses, more women living longer, and very importantly reduce the toxicity of any treatment.

RACHAEL BROWN: How did scientists work out which cells were inhibiting patients' immune systems?

MICHAEL QUINN: Well we've been aware for a long time that everyone recognises that cancer is a foreign body and that we mount an immune response to this cancer and we've often wondered why this is ineffective.

And what we've been able to show in the last four or five years is that there are other cells within the body that are inhibiting this normal immune response, and importantly that these cells are actually cycling every eight to 12 days, so we have our own rhythm of immunity. And it's that observation that we can interfere with that rhythm and get good results that I think is very exciting.

RACHAEL BROWN: And that barrier that these cells are putting up ends up killing four out of five patients within five years?

MICHAEL QUINN: That's the terrible statistic around ovarian cancer. So this is a really bad cancer and it's one that we've got to do something about. And this I think is a novel approach. It's got good science attached to it and let's hope that that translates to the bedside.

RACHAEL BROWN: Tell me about this trial that you've begun this week.

MICHAEL QUINN: The trial that we're doing is in women with ovarian cancer who've had recurrence after two treatments with chemotherapy. We have to take blood every

second day and we do that for two weeks and that allows us to look at the woman's own immune cycling and work out exactly when to deliver the very, very low-dose chemotherapy by mouth that will knock off these inhibitory cells.

RACHAEL BROWN: And if this trial works, what cancers could it be applied to?

MICHAEL QUINN: Any cancer, so any solid tumour; bowel cancer; breast cancer; lung cancer, ovarian cancer, uterine cancer. So any of these non-blood cancers.

RACHAEL BROWN: So how many lives could be spared?

MICHAEL QUINN: Oh we're talking hundreds of thousands of lives.

RACHAEL BROWN: Every year?

MICHAEL QUINN: Every year. It's going to take about 18 months to two years to finish the trial, analyse all the results, do the basic science which we are with the Department of Immunology at Monash University.

And that of course takes time and money and effort so I encourage your listeners to come along on Sunday morning to the Tan and walk around the Tan and do that for ovarian cancer research. To provide us with one clinical research nurse costs \$80,000 a year so it's a lot of money.

TONY EASTLEY: Oncologist Professor Michael Quinn ending that report by Rachael Brown.

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Scientists manipulate immune system to fight cancer

Posted Thu Mar 12, 2009 1:45pm AEDT

Updated Thu Mar 12, 2009 1:53pm AEDT

Melbourne researchers think they have found a way to turn off the cells that prevent cancer patients' immune systems from beating previously untreatable tumours.

The Women's Cancer Foundation and Monash University in Melbourne have just begun an 18-month trial using low dosage chemotherapy pills. They say it could save hundreds-of-thousands of lives each year.

Professor Michael Quinn from Melbourne's Royal Women's Hospital says the new method involves using the patient's own immune system, and less toxic cancer treatments.

"What we're hoping is that by using this particular method of synchronising the patient's own immune system, that we'll be able to get better responses, more women living longer, and very importantly reduce the toxicity of any treatment," he said.

He says while scientists have long known the body mounts an immune response to cancer, they did not know why this response was ineffective.

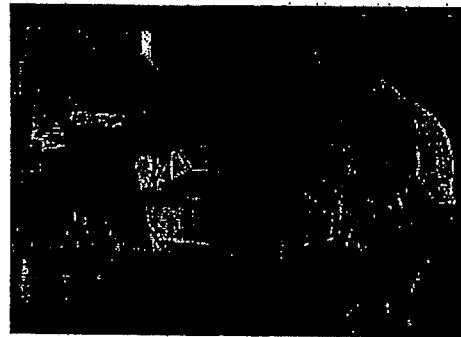
"What we've been able to show in the last four, five years is that there are other cells within the body that are inhibiting this normal immune response, and importantly that these cells are actually cycling every eight to 12 days, so we have our own rhythm of immunity," he said.

"It's that observation, that we can interfere with that rhythm and get good results, that I think is very exciting."

Professor Quinn says four out of five patients die within five years due to the barricade put up by the inhibiting cells.

"That's the terrible statistic around ovarian cancer. So this is a really bad cancer and it's one that we've got to do something about," he said.

"And this I think is a novel approach. It's got good science attached to it and let's hope that translates to the bedside."



If the trial is successful it could be used to treat various types of cancer.

• [Map: Melbourne 3000](#)

Professor Quinn is involved in a trial beginning this week, which will look at ovarian cancer patients who have had two treatments with chemotherapy but still suffered a recurrence.

The researchers will take blood samples from the women every second day for two weeks, so they can get a good picture of the cycles of each woman's immune system.

The scientists will then use the information to determine when each woman should orally take an extremely low dose of chemotherapy which will kill the inhibitory cells.

Professor Quinn says if the trial is successful it could be used to treat other types of cancer.

"Any solid tumour, bowel cancer, breast cancer, lung cancer, ovarian cancer, uterine cancer. So any of these non-blood cancers," he said.

He says the research will take up to two years to finish the trial and analyse all the results and it is a costly process.

"To provide us with one clinical research nurse costs \$80,000 a year so it's a lot of money," he said.

On Sunday the Women's Cancer Foundation are hosting a fundraising walk in Melbourne to raise money for the research.

-Adapted from a report by Rachael Brown for AM.

Tags: diseases-and-disorders, cancer, medical-research, vaccines-and-immunity, ovarian-cancer, australia, vic, melbourne-3000

Melbourne researchers pioneer radical ovarian cancer treatment

EARLY results from a new cancer treatment pioneered in Melbourne show that advanced ovarian cancer can be fought to a standstill — an against-the-odds result that could point to a radical new way of beating other cancers.

Researchers from the Royal Women's Hospital and Monash University say they are increasingly excited about the trial, which began last year.

The research comes as new national figures on ovarian cancer showed that almost two-thirds of Australians diagnosed with the disease will not be alive five years later.

Professor Michael Quinn, from the Royal Women's Hospital's cancer unit, is leading a team testing "immune modulation" therapy.

It works on the theory that the immune system has a 10 to 14-day cycle, during which it emits "inhibitor cells" that stop the body fighting cancer.

The team gives small, tightly targeted chemotherapy doses at exactly the right time in the cycle to block the inhibitor cells and boost the body's defence

Since last year they have given the therapy to seven women with advanced, recurrent ovarian cancer, while also working with Monash University's department of immun-

Several of the women have responded positively to the treatment, Professor Quinn said. "These are very, very promising results," he said. "The tumours have stopped growing! — that's all we had hoped for. I don't think this is the magic bullet yet but it's cor-

tainly enough for us to continue our work."

The treatment avoids almost all the debilitating side effects of chemotherapy, allowing patients to live more normal lives. One of the patients is 44-year-old Melissa Campbell, who went to her doctor four years ago with back pain and a bloated stomach — and came

back with a diagnosis of advanced ovarian cancer.

Since then, the cancer has recurred twice, putting her through surgery and excruciating chemotherapy and radiation therapy, as well as another experimental drug with severe side effects.

But she said the new treatment, which began last April,

had been a totally different experience. "It hasn't gotten rid of [the tumour]," she said. "But it hasn't gotten worse. It's keeping it under control, and fingers crossed it will get rid of it down the track."

"It's so much easier compared to the other times it does have a few side effects, but they are a piece of cake compared to

standard chemo or some of the other drugs."

The chemo comes in a simple pill a few days a fortnight, rather than a trip to hospital being hooked up to a drip. One drawback is having a blood test every two days.

Mr Campbell said one of the biggest problems with ovarian cancer was the lack of knowledge.

[illegible]

lodge among both the pur and doctors, its vague sytoms mean it is often gnot until it is well advanced.

Most women thought it could be picked up with a psp smear.

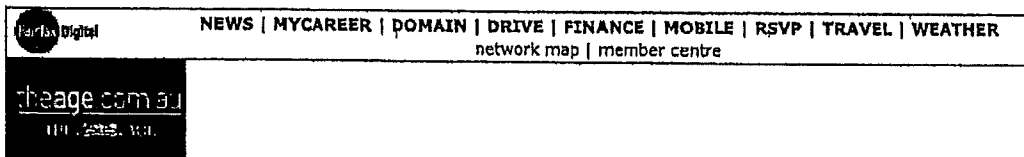
Professor Pugh said: "I team was still on 'a learn curve' but there was alrea preliminary work to se if treatment could be used melanoma patients.

Australian Institute of Hca and Welfare figures releae today show a slight increae survival levels of ovarian can patients, but it is still among the biggest cancer killers.

The latest figures, from 201 show there were 1225 cases ovarian cancer diagnosed Australia, meaning an avers three women were diagnos with the disease every day.

An average of two per d died from ovarian cancer. Fo out of 10 women diagnos with ovarian cancer betwe 2000 and 2005 were alive fi years after their diagnosis, c improvement on the 33 per c

The research is sponsored by Monash University and the Women's Cancer Foundation. The WCF is holding the "4 Can Walk It Out" walk and fundraiser at the Sun at 10am this Sunday. www.womenscancerfoundation.org.



Cancer discovery heads for trials

By Rebecca Urban
Biotechnology Reporter
October 25, 2005

A MELBOURNE scientist has made a discovery that could revolutionise the way chemotherapy is administered and improve cancer survival rates.

The discovery, which centres on the immune system's response to cancer cells, has been approved for independent studies at two Melbourne hospitals and a leading cancer centre in the United States.

"We think the potential is very high," said Associate Professor Michael Quinn, director of oncology at the Royal Women's Hospital and one of several oncologists who have been collaborating on the project.

"The concept is that chemotherapy may work more effectively if you can syncretise it with the patient's immune response. It's a very exciting concept."

The project originates from the work of Melbourne scientist Martin Ashdown, who has discovered the existence of a regulated immune response cycle in cancer patients.

Oncologists are hoping that the oscillating cycle, which repeats itself approximately every 14 days, might be used to establish the most effective time to administer chemotherapy.

The Mayo Clinic in the US, which is independent from the project, is believed to be impressed by the research and will start using the cycle to treat cancer patients in a clinical trial to start before Christmas.

The study will attempt to gauge the cycle's impact on the efficacy of standard chemotherapy.

Both the Austin and Royal Women's hospitals in Melbourne are monitoring patients to confirm that the cycle is universal and plan to start clinical trials next year.

Mr Ashdown discovered the cycle in 2002 and it has since been identified in mice with malignant tumours as well as a group of patients with advanced cancer.

He believes the cycle could explain why only a small portion, typically about 7 per cent, of late-stage cancer patients completely respond to chemotherapy.

These so-called "miracle recoveries" seen in terminal patients could be the result of the chemotherapy being fortuitously administered at the right time in the immune cycle, he said.

"We believe that the chemotherapy actually releases the patient's immune system from regulation, giving it the freedom to attack the cancer," he said.

"From animal experiments — ours and other published experiments — it may be that only one dose of chemotherapy is needed to kill the cancer, providing that you administer the treatment at the right time."

Mr Ashdown's project is 65 per cent owned by the listed biotech company Genetic Technologies. The company is reviewing the project, called ImmunAid, to establish a path to commercialisation.

In its annual report, which was mailed to shareholders yesterday, the company said possible outcomes of the research included developing new treatment strategies using existing drugs or the development of new drugs and diagnostic tests.

It is believed the project has also attracted the interest of some of the world's largest pharmaceutical companies.

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UK NEWS

CANCER 'CODE' IS CRACKED

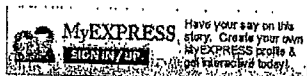


Sunday March 7, 2010

By Lucy Johnston

Have your say (0)

Researchers believe they have succeeded in halting the spread of advanced cancer



SCIENTISTS believe they have made a major breakthrough in cancer treatment after cracking the "code" behind the disease.

They have discovered the body's immune system can kill cancer cells within a window occurring every 12 to 14 days.

By giving low-dose treatment at exactly the right time, researchers believe they have, against the odds, succeeded in halting the spread of advanced cancer.

Professor Michael Quinn has led the trial in patients with advanced ovarian cancer and suggests it could signal the most exciting development since the introduction of chemotherapy in the Fifties.

While he points out that it is still a theory, he said: "This is astonishing and could influence the treatment of all solid tumours in the future. We hope it will revolutionise the treatment of cancer." Professor Quinn and his team reviewed 63 papers involving more than 1,200 patients since 2000.

They discovered that sufferers had about a 1-in-12 chance of responding to chemotherapy. During further studies they found the body has a fortnightly immune cycle during which it "switches on and off".

When the immune system turns off, it releases "inhibitory cells" which prevent it fighting disease, including cancer.

Professor Quinn and his team in Melbourne, Australia, target chemotherapy when the immune system is not working to knock out "inhibitory cells", dramatically improving patients' chances of recovery.

The treatment is in pill form and patients avoid almost all the debilitating chemotherapy side effects.



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Professor Quinn, originally from Glasgow, said: "Everyone, including non-cancer patients, has an immune cycle which fluctuates every 12 to 14 days.

"That's why if someone in the family comes in with a cough or cold, only some members of the family will develop it. The immune system also attacks cancer cells, which is why we need to give chemotherapy on the right day."

"The concept is sensational. If you can treat people at the right time it could dramatically improve their chance of a successful outcome. The research is still in its early stages, however if we are proved right this method of treatment could be applied to all cancers and in fact all diseases."

Since last year Professor Quinn and his team at Royal Women's Hospital and Monash University, Melbourne, have given the therapy to seven women. Their advanced, recurrent ovarian cancer is almost impossible to treat successfully. Several responded positively and their tumours have stopped growing. Professor Quinn added: "These are very, very promising results."

One patient, Melissa Campbell, went to her doctor four years ago with back pain and a bloated stomach, and was diagnosed with advanced ovarian cancer.

The disease recurred twice, and she has endured surgery, chemotherapy and radiotherapy, as well as severe side effects from another experimental drug.

The 44-year-old said the new treatment had been a totally different experience: "It's keeping it under control, and fingers crossed it will get rid of it down the track. It's so much easier compared with the other times."

The treatment is a pill taken for a few days every fortnight rather than the patient being attached to a drip in hospital. Blood tests are also carried out every two days to assess the immune system.

Preliminary work is now underway to use the same methods to treat patients with skin cancer. Professor Peter Johnson, Cancer Research UK's chief clinician, welcomed the news: "We know the immune system may be influential in treating many cancers."

"Any research that helps our understanding may hold promise for the future."



8 November 2007

To Whom It May Concern:

I am Professor Andrew Wilks FTSE, the Chief Scientific Officer for Cytopia. I am the founder of Cytopia P/L and the group's Chief Scientific Officer. Cytopia's mission is to become a leading discoverer of targeted small molecule therapeutics for diseases such as cancer, cardiovascular and immune disease, delivering drug candidates at various stages of clinical development.

Following extensive discussions with several key scientists at ImmunAid I have become familiar with the principles associated with the ImmunAid work promoted particularly by Martin Ashdown. These are interesting concepts and I see how the successful application of the outcomes of this research might lead to the exploitation of the purported immune system cycle. The ImmunAid team's research may have important ramifications for our own work in the treatment of cancer and immune disease.

I have discussed with Martin the possibility of incorporating the monitoring of CRP levels in some of our clinical trial patients when patient agreement can be negotiated. If these results are informative, we have considered the notion implementing the use of the immunological cycle to treat a small number of such patients (following appropriate ethics approval, naturally).

The major potential advantages associated with the protocol are

- The treatment may be more effective than current therapy courses that do not address immune regulation;
- That side effects of normal cancer and auto-immune disease therapies may be reduced, allowing the development of safer protocols;
- Products that would otherwise result in unacceptable side effects could in theory be developed;
- Substantially increase the rate at which new products could be introduced due to increased efficacy and reduced toxicology
- Enable many of the less toxic and less expensive chemotherapeutics to be used substantially reducing the costs of treatments.

Should any of these benefits arise from the current trials underway throughout the world I believe that we would also be keen to introduce the benefits into our drug development programme. I am very supportive of further work on this

Immune cycle, and greatly anticipate important proof of concept studies that may come from the ImmuneAid work.

Sincerely,

A handwritten signature in black ink, appearing to read 'A. Wilks'.

Professor Andrew F. Wilks FTSE

Chief Scientific Officer, Cytopia Ltd.



200 First Street SW
Rochester, Minnesota 55905
507-284-2511

Svetomir N. Markovic, M.D., Ph.D.
Department of Internal Medicine
Division of Hematology

May 22, 2007

Mr. Martin L. Ashdown
Chief Research Scientist
Immunaid Pty Ltd
60-70 Hanover Street
P.O. Box 115
Fitzroy VIC 3065
AUSTRALIA

Dear Mr. Ashdown,

I am writing this letter in support of your efforts to further our collective understanding of the role of T-regulatory cell oscillations in humans as they may pertain to disease. I have been struck by your observations and their increasingly recognized validity by the scientific community. In our own ongoing, preliminary experience, time delivery of chemotherapy intended to disrupt regulatory T-cell function appears to offer added therapeutic benefit in the treatment of metastatic melanoma.

I sincerely hope that you continue your work in this vein and bring us closer to a more rational design in cancer therapy utilizing this powerful observation.

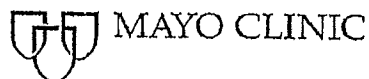
Sincerely yours,

A handwritten signature in dark ink, appearing to read 'S. Markovic'.

Svetomir N. Markovic, M.D., Ph.D.
Chair, Melanoma Study Group
Mayo Clinic Cancer Center

SM:le

By email 3/10/05
Oncologist / Immunologist



200 First Street SW
Rochester, MN 55905
507-284-2511

Svetomir N. Markovic, M.D., Ph.D.
Department of Internal Medicine
Division of Hematology

October 3, 2005

ATTN: Scientific Advisory Review Panel
RE: Clinical investigation studies: Royal Women's Hospital Project 2003/36
Investigators: Michael Quinn and Martin Ashdown
RE: Austin Hospital/Ludwig Institute Project 2004/02087
Investigators: Jonathan Cebon and Martin Ashdown

To Whom It May Concern:

I fully endorse the work of Martin Ashdown and Michael Quinn.

Martin Ashdown has presented a coherent scientifically rational hypothesis which is consistent with clinical experience and the collected data. In addition, this data is also consistent with the current and emerging understanding of the dynamic, sequential, and time dependent nature of the immune system and its role in the chronic course of neoplastic disease.

The discovery of the postulated regulated immune response cycle in the cancer patient is potentially of immense clinical significance with profound public health implications. Consequently it must be pursued with vigor and tested clinically as soon as possible. We look forward to collaborating on this front and endorse a move to efficacy trials. As this approach would use standard chemotherapeutic agents administered in a timed fashion with respect to the status of the immune system, barriers to carrying out this sort of trial are minimal. In collaboration with Martin Ashdown we are currently pursuing a phase II clinical trial using conventional chemotherapy for the treatment of metastatic malignant melanoma at the Mayo Clinic in Rochester, Minnesota.

Thank you.

Sincerely,

Svetomir N. Markovic, M.D. Ph.D.
Chair
Melanoma Group
Mayo Clinic

Attachment 9

April 18, 2010

To whom it may concern,

I am Dr Andrew Robinson, Senior Lecturer in Applied Statistics with the Department of Mathematics and Statistics, University of Melbourne. I have more than twenty years of professional experience in data analysis and the application of statistical modeling in a variety of subject-matter fields, including the analysis and meta-analysis of oncology trial data.

I have read European patent application number 04761461 entitled "Method of Therapy" and I understand its quantitative and modeling elements. I am not positioned to judge its biochemistry.

On April 10, 2006 I was asked to analyze C-reactive protein (CRP) time-series data for a small set of anonymous cancer patients by Martin Ashdown. The analysis was conditioned on the existence of a cycle in CRP, and the goal was to estimate the periodicity of the cycle and the temporal location of the peaks. Since that date I have extensively analyzed the CRP trajectories for more than twenty such patients drawn from several clinics in Australia and the United States, and constructed statistical models that, assuming a cycle in the trajectory, permit the estimation of the temporal period and the location of the times at which treatment might be expected to have the greatest effect. Despite the natural biological variation, I have seen evidence for the claim of a cycle in the trajectory of biomarker measures for cancer patients.

Conditional on the information contained in application 04761461 as filed, I believe that it would have been straightforward in October 2004 to analyse a time series of cell counts or biomarker levels to detect, within the limits of natural biological variation, whether a particular cell or biomarker were cycling in a patient. Furthermore, if there were evidence of such cycling, then it would also have been straightforward, within the limits of natural biological variation, to then correlate clinical outcomes to optimize the time point in the cycle of a particular cell or biomarker at which to administer a particular drug.

In closing, if I or those for whom I am responsible were to contract cancer then I would most certainly wish to analyse my immune system cycle to enhance the chance of any chemotherapy effectively treating the disease.

Yours sincerely,



Andrew Robinson
Senior Lecturer, Applied Statistics.